REMARKS

Reconsideration of the rejections set forth in the Office action mailed November 1, 2002 is respectfully requested.

I. Amendments

The specification has been amended to explicitly include subject matter incorporated by reference in the specification as filed. Specifically, the specification incorporated by reference a co-owned patent, U.S. Patent No. 5,185,444, stating that "As shown in the reference, several types of nonionic linkages may be used to construct a morpholino backbone." (See page 8, lines 27-30 of the instant specification.) The amended paragraph includes two such linkage structures as set forth in claims 4 and 6, respectively, of the incorporated patent.

Independent claim 28 has been amended to explicitly recite in the preamble that the method is used "in a patient", as previously recited in the body of the claim.

Claims 29 and 42 have been amended to define the variables used in the depicted structures, as defined in the specification at page 8, line 39 to page 9, line 6.

Claims 30, 38 and 43 have been amended to include embodiments of the linkage structure which are disclosed in U.S. Patent No. 5,185,444, incorporated by reference, which have been explicitly included in the specification by the present amendment.

Claim 38 has also been amended to depend from claim 28, and for clarity. Support for the phrase "effective to deliver between about 0.5 and 2 mg antisense compound into the vessel tissue" is found at page 11, lines 9-12 of the specification.

Claim 34 has been amended to recite that the amount of antisense compound administered is between 5 and 20 mg, as stated at page 11, lines 11-12 of the specification.

Several claims are amended to correct typographical errors.

No new matter is added by any of the amendments.

II. Rejections under 35 U.S.C. §112, First Paragraph

Claim 34 was rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

In response, applicants have amended claim 34 to comport with the specification at page 11, lines 11-12.

In view of the foregoing, the applicants submit that amended claim 34 complies with the requirements of 35 U.S.C. §112, first paragraph.

III. Rejections under 35 U.S.C. §112, Second Paragraph

Claims 29 and 42 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner noted that the claims did not provide definitions of the variables Pi, Pj, X, Y_1, Y_2, and Z used in the structures shown in the claims.

Claims 29 and 42 have been amended to provide definitions of these variables, as provided in the specification at page 8, line 39 to page 9, line 6.

In view of the foregoing, the applicants submit that amended claims 29 and 42 comply with the requirements of 35 U.S.C. §112, second paragraph.

IV. Rejections under 35 U.S.C. §102(e) and §102(b)

Claims 28, 32, 34-36, and 41 were rejected under 35 U.S.C. §102(e) as being anticipated by Zalewski *et al.*, U.S. Patent No. 6,133,242, and under 35 U.S.C. §102(e) as being anticipated by Zalewski *et al.*, U.S. Patent No. 6,159,946. These rejections are respectfully traversed for the following reasons.

The standard for lack of novelty, that is, for anticipation, is one of strict identity. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F2d 1367, 231 USPQ 81, 90 (Fed. Cir. 1986); *In re Donohue*, 766 F2d 531, 226 USPQ 619, 621 (Fed. Cir. 1985). To anticipate a claim for a patent, a single prior source must contain all its essential elements.

A. The Invention

Each of independent claims 28 and 41 includes, as a key element, "a morpholino antisense compound having...uncharged, phosphorus-containing intersubunit linkages".

B. The Prior Art

The only occurrence of the term "morpholino" in the Zalewski patents appears at column 8, lines 7-12 of the '242 patent, and at column 7, lines 1-6 of the '946 patent, in the following context (emphasis added):

> Additional nuclease linkages [sic; probably intends "nuclease resistant linkages"] include phosphoroselenoate, phosphorodiselenoate, phosphoroanilothioate, phosphoranilidate, alkylphosphotriester such as methyl- and ethylphosphotriester, carbonate such as carboxymethyl ester, carbamate, morpholino carbamate, 3'-thioformacetal....

The only morpholino compounds disclosed, therefore, are compounds having "morpholino carbamate" linkages, not "uncharged, phosphorus-containing intersubunit linkages".

Neither reference discloses "a morpholino antisense compound having (i) from 8 to 40 nucleotides, including a targeting base sequence that is complementary to a region that spans the start codon of a human c-myc mRNA gene, and (ii) uncharged, phosphorus-containing intersubunit linkages", as required by the independent claims.

Since neither reference discloses all of the elements set out above in claims 28 and 41 and dependent claims 32 and 34-36, the claims cannot be anticipated by either of these references. In view of this, the applicants respectfully request the Examiner to withdraw the rejection under 35 U.S.C. §102(e) and §102(b).

V. Rejections under 35 U.S.C. §103

Claims 28-48 (all pending claims) were rejected under 35 U.S.C. §103(a) as being unpatentable over Zalewski *et al.*, cited above, in view of Kobayashi *et al.* (*Osaka Daigaku Zasshi* **47**(6-12), Abstract, 1995), Summerton *et al.* (U.S. Patent No. 5,378,841), Agrawal *et al.* (U.S. Patent No. 5, 912,332), and Wolff *et al.* (U.S. Patent No. 6,133,242). The rejections are respectfully traversed in light of the following remarks.

A. The Invention

The applicant's invention, as embodied in independent claim 28, is directed to a method of for treating a vascular injury site by reducing restenosis at the site. The method comprises administering to a patient, by intravascular delivery directly to the vascular injury site, a morpholino antisense compound having (i) from 8 to 40 nucleotides, including a targeting base sequence that is complementary to a region that spans the start codon of a human c-myc mRNA gene, and (ii) uncharged, phosphorus-containing intersubunit linkages, in an amount effective to reduce restenosis in the patient.

The claimed method was effective to inhibit restenosis in two animal models, as shown in Kipshidze *et al., Catheterization and Cardiovasc. Intervention* **54**:247-56 (Oct 2001) and

Kipshidze *et al., J. Am. Coll. Cardiology* **39**(10):1686-91 (2002), of which copies are enclosed.

More significantly, a recently completed Phase II clinical study, described in the enclosed Declaration executed by co-inventor Dr. Dwight Weller, showed efficacy in a patient population having existing recurrent restenosis following PTCA, and selected based on criteria targeting patients with a high probability of restenosis. As shown in the Declaration, patients receiving a dose of oligomer determined to be at a therapeutic level showed significantly less reocclusion than patients receiving a subtherapeutic dose or receiving no oligomer. No drug related serious adverse effects were observed.

B. The Cited Art

Zalewski *et al.* disclose various types of modified oligonucleotides. As discussed above, however, Zalewski *et al.* do not disclose "administration of antisense oligonucleotides comprising a morpholino and modified phosphorus containing intersubunit linkages" (Office Action, page 7).

The patents do disclose, in working examples, the use of a phosphorothioate-linked oligonucleotide targeting c-myc mRNA in an vivo porcine model of coronary angioplasty. The data showed that the oligonucleotide "significantly reduced neointimal formation" in this animal model (Example 3 in the '242 patent; Example 11 in the '946 patent).

The cited reference does not, however, disclose efficacy of the phosphorothioate oligonucleotide in a patient population.

As reported in the enclosed paper by Kutryk *et al.* (*J. Amer. Coll. Cardiology* **39**:281-7, 2002), which is discussed in the enclosed Declaration, a clinical trial employing this phosphorothioate oligonucleotide failed to show any efficacy in inhibiting post-PTCA restenosis in a patient population.

Kobayashi *et al.* is cited for its disclosure of a phosphorothioate oligonucleotide having a 27-nucleotide sequence which includes the 20-nucleotide sequence disclosed by the applicants as SEQ ID NO: 1. The phosphorothioate oligonucleotide of Kobayashi was reported to reduce the expression of c-myc in vitro, and to suppress the tumor growth of gastric cancer cells and colon cancer cells transplanted in nude mice.

Summerton *et al.* discloses uncharged-backbone morpholino oligomers and their benefits

over native RNA or DNA oligonucleotides as antisense agents.

Agrawal *et al.* is cited for its disclosure of a triethylene glycol solubility-enhancing group.

Wolff *et al.* is cited for its disclosure of stents, including biodegradable stents and stents containing diffusible therapeutics.

C. Analysis

The CAFC held, in *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988), that "Recognition of need, and difficulties encountered by those in the field, are classical indicia of unobviousness." As stated in a preliminary report assessing the safety and pharmacokinetics of the Zalewski oligonucleotide (Roque *et al.*, Antisense & Nucleic Acid Drug Dev. 11:99-106, 2001; copy enclosed), "Coronary restenosis remains a vexing clinical problem" (page 99, Introduction). The paper notes some of the perceived difficulties, including the "more complex human atherosclerotic lesions" as compared to porcine coronary arteries in model studies (paragraph bridging pages 103-104). These difficulties are further illustrated by the failure of the Zalewski oligonucleotide to show any effectiveness in the clinical trial discussed in the Kutryk *et al.* report.

In the same decision, the Court further observed that the "consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that the invention should be carried out and would have a reasonable likelihood of success, viewed in light of the prior art. Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure."

Zalewski and Kobayashi discuss the effectiveness of phosphorothioate oligonucleotides targeting c-myc in reducing restenosis, or inhibiting growth of transplanted tumor cells, respectively, in animal models. Summerton *et al.* discloses uncharged morpholino oligomers and discusses their benefits in general. However, these references in combination do not provide a reasonable expectation that a morpholino oligomer as presently claimed would effectively inhibit restenosis at a vascular injury site in a patient, as demonstrated by the data presented in the enclosed Declaration.

Wolff *et al.* describes stents containing diffusible therapeutics, as well as biodegradable stents. However, there is no suggestion to include as such a diffusible therapeutic a morpholino oligomer as recited in independent claim 41; nor do the references provide, for the reasons

discussed above, a reasonable expectation that such an oligomer would effectively inhibit restenosis in a patient.

In view of the foregoing, the applicants respectfully request the Examiner to withdraw the rejections under 35 U.S.C. §103(a).

VI. Conclusion

In view of the foregoing, the applicant submits that the claims now pending are now in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 838-4403.

Respectfully submitted,

LeeAnn Gorthey

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LeeAnn Gorthey
Registration No. 37,337

Correspondence Address:
PAYOR NUMBER 22918
PHONE: (650) 838-4403
FAX: (650) 838-4350